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Color Doppler Ultrasonographic Evaluation of the Ureteral Jet Angle to Detect Vesicoureteral Reflux in Children

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Running title: Color Doppler ultrasonographic evaluation of the ureteral jet angle for vesicoureteral reflux

Key words: children, color Doppler, ultrasonography, ureteral jet, vesicoureteral reflux

Abstract:

Purpose: Vesicoureteral reflux is the most common urinary tract abnormality in children. Although voiding cystourethrography is the gold standard for diagnosing reflux, it is invasive. The aim of the present study was to evaluate color Doppler ultrasonographic measurements of the ureteral jet angle (UJA) as a non-invasive screening tool for detecting reflux.

Materials and Methods: We retrospectively evaluated 125 pediatric patients, 250 renal units, who presented with urinary tract infections or hydronephrosis. All patients underwent color Doppler ultrasonography and voiding cystourethrography. The UJA was measured as the angle between the direction of the ureteral jet and interureteral ridge.

Results: Reflux was diagnosed in 80 patients, 117 renal units. The mean value of the UJA was significantly higher in refluxing units (67.9 ± 18.7°) than in non-refluxing units (47.8 ± 17.3°, $p < 0.0001$). The angle value in each reflux grade became significantly higher according to its grade ($p < 0.0001$). The overall ability of the UJA to detect grade III-V or grade IV, V reflux, as given by the area under the receiver-operating characteristic curve, was 0.81

or 0.88, respectively. A cut-off angle ≥ 55° detected grade III-V or grade IV, V reflux with a sensitivity of 85.5% or 94.7%, respectively. A cut-off angle ≥ 70° diagnosed grade IV, V reflux with a sensitivity of 81.6% and specificity of 82.7%.

Conclusions: Color Doppler ultrasonographic measurements of the UJA represent a simple and non-invasive method that is applicable as a screening tool to detect high grade vesicoureteral reflux in children.

249 words

Introduction:

Vesicoureteral reflux (VUR) is defined as the retrograde flow of urine from the bladder into the upper urinary tract, and is the most common urinary tract abnormality in children[1)]. It is responsible for renal scarring, and can be associated with congenital renal dysmorphism[1)].

The basis of VUR detection lies in demonstrating the retrograde passage of an imaging contrast material from the bladder to the ureter and renal pelvicalyceal system. Although X-ray voiding cystourethrography (VCUG) is the gold standard for diagnosing VUR, it is invasive and requires the use of ionizing radiation and urethral catheterization[1)]. Therefore, a radiation-free and catheter-free non-invasive method to detect VUR is desired.

Primary VUR has been attributed to early ureteral budding in embryology of the ureterovesical junction (UVJ)[1)]. Therefore, higher grade VUR has a more laterally placed ureteral orifice and shorter intramural ureteral tunnel[1)]. We hypothesized that a bolus of urine (the ureteral jet) is ejected more perpendicularly to the bladder base through the ureteral orifice in higher grade VUR (Figure 1 A).

Color Doppler ultrasonography allows for the clear and simple visualization of the ureteral jet as it enters the bladder[2)]. In the present study, we defined the ureteral jet angle (UJA) as the angle between the direction of the ureteral jet and interureteral ridge (Figure 1 B), and aimed to evaluate the efficacy of color Doppler ultrasonographic UJA measurements as a non-invasive screening tool for detecting VUR in pediatric patients.

Materials and Methods:

We retrospectively evaluated 125 pediatric patients (73 boys, 52 girls), 250 renal units, who presented with urinary tract infections (UTI) or hydronephrosis between 2010 and 2013. All patients routinely underwent ultrasonography and VCUG to evaluate their primary diseases. Patients were aged between 1 month and 14 years (median: 3.0 years). Children with lower urinary tract abnormalities such as a posterior urethral valve, ureterocele or neurogenic bladder associated with spina bifida were excluded from this study.

Ultrasonographic examinations were performed using a curved array probe in the frequency range of 5 to 8 MHz (Toshiba Aplio 500, Otawara, Japan). Patients were asked to ingest a large amount of liquid, and were well hydrated at the time of the examination. After systematic evaluations of the kidney, ureter, and bladder, UJA was measured using a color Doppler scanner for approximately 5 to 10 minutes. Children were examined in the supine position without sedation, and measurements were obtained when the bladder was filled with urine at more than approximately half of the estimated bladder capacity3). The bladder was visualized in the transverse plane to simultaneously evaluate both ureteral orifices at the trigonal level. The probe was fixed perpendicularly, and the color Doppler mode was applied to visualize ureteral jets. UJA was measured as the angle between the direction of the ureteral jet and interureteral ridge (Figure 1 B). Two examiners performed UJA measurements based on the same unified method. VCUG was performed as the standard method, and VUR was graded into five grades following the international classification4). Ultrasonography and VCUG were performed by examiners who were blinded to each other's results.

Data were expressed as means ± standard deviation, absolute values, fractions, or 95% confidence intervals (CI). The Mann-Whitney test or Kruskal-Wallis test was used to compare two or multiple groups, respectively. Spearman's rank correlation was used to identify the strength of the relationship between UJA values and VUR grades. The significance of

UJA to detect VUR and the best threshold to distinguish between them were assessed based on receiver-operating characteristic (ROC) curves. All data were considered significant at $p < 0.05$. Statistical analyses were performed using JMP® version 11.2.0 (SAS Institute Japan Ltd., Tokyo, Japan).

The Ethical Research Committee and Institutional Review Board approved this study (No. 2012-177).

Results:

All patients underwent color Doppler ultrasonographic UJA measurements without complications. VCUG revealed VUR in 80 patients (64.0%), 117 renal units (46.8%) (Table 1). Among these patients, grade I was detected in 16 renal units (13.7%), grade II in 30 (25.6%), grade III in 32 (27.4%), grade IV in 30 (25.6%), and grade V in 9 (7.7%).

The mean value of UJA was significantly higher in refluxing renal units (67.9 ± 18.7°) than in non-refluxing units (47.8 ± 17.3°, $p < 0.0001$) (Figure 2 A). On the other hand, no significant differences were observed in UJA values according to patient gender (male: 55.8 ± 21.2°, female: 59.8 ± 19.6°, $p = 0.09$) or age (< 3 years old: 57.3 ± 21.3°, ≥ 3 years old: 57.7 ± 19.9°, $p = 0.74$).

The mean values of UJA in each VUR grade were 47.8 ± 17.3°, 57.6 ± 14.5°, 61.2 ± 17.1°, 63.8 ± 17.4°, 78.1 ± 16.9°, and 88.6 ± 9.9° in grades 0, I, II, III, IV, and V VUR, respectively (Figure 2 B). A positive correlation was detected between UJA values and VUR grades ($p < 0.0001$).

The overall ability of UJA measurements to detect grade I-V, grade III-V, or grade IV, V VUR, as given by the area under the ROC curve, was 0.79, 0.81, or 0.88, respectively (Figure 3).

A cut-off UJA value ≥ 50° or ≥ 55° correctly detected grade III-V VUR with a sensitivity of 89.9% (95% CI: 81.7-94.9%) or 85.5% (95% CI: 76.8-91.6%), respectively (Table 2 A). A cut-off UJA value ≥ 55° or ≥ 60° correctly detected grade IV, V VUR with a sensitivity of 94.7% (95% CI: 83.5-98.5%) or 92.1% (95% CI: 80.2-97.2%), respectively (Table 2 B). Furthermore, a cut-off ≥ 70° diagnosed grade IV, V VUR with a sensitivity of 81.6% (95% CI: 68.4-90.4%) and specificity of 82.7% (95% CI: 80.2-84.4%).

In this study cohort, a cut-off UJA value ≥ 50° or ≥ 55° would have missed only 1 (1.8%) or 3 (5.5%) of 55 patients who had grade III-V VUR in the at least one side, respectively. A cut-off UJA value ≥ 55° or ≥ 60° would have missed only 1 (3.2%) of 31 patients who had grade IV, V VUR in the at least one side.

Discussion:

The incidence of VUR (64.0%) in this study was higher than the expected incidence rate of VUR[1)]. Its main reason is thought that a lot of severer patients are referred to us, because our institutions are advanced treatment medical centers in our districts. Indeed, a total of 102 of 125 patients (81.6%) developed febrile UTI before the examination, 33 of whom (32.4%) had multiple episodes.

X-ray VCUG is the gold standard for diagnosing VUR; however, it is invasive and requires radiation exposure and urethral catheterization in pediatric patients[1)]. Children are more sensitive to radiation injury than adults, and concerns have been expressed regarding radiation exposure for long-term cancer development in children. Liao et al. recently reported that the overall cancer risk of a VCUG cohort was significantly higher (1.92-fold) than that of a non-VCUG cohort[5)]. Urethral catheterization is not tolerated well by children and their parents. Dysuria, hematuria, UTI, and stricture disease may develop as a result of catheterization. Children invariably recall repeated VCUG as their worst experience rather than the surgical procedure for VUR[6)]. It is also stressful for physicians and medical imaging stuff. Therefore, a radiation-free and catheter-free non-invasive method is needed in order to detect VUR, and X-ray VCUG should be performed in selected patients.

Several other imaging modalities have been widely used to diagnose VUR, in which the retrograde flow of urine is directly detected. Radionuclide voiding cystography is one of the common diagnostic modalities of VUR[1)]. It has lower radiation exposure than VCUG, but also requires urethral catheterization to inject a radionuclide agent into the bladder, and the anatomical details depicted are inferior. Echo-enhanced voiding urosonography or direct magnetic resonance VCUG are radiation-free modalities with sensitivities of 57-100% or 97% and specificities of 85-100% or 96%, respectively[7,8)]. However, both of these modalities require catheterization for the administration of contrast agents into the bladder. Furthermore, the availability of MRI scanners is limited, intravenous sedation is needed in order to avoid artifacts produced by patient motion in young children, and this modality is expensive.

Several radiation-free, catheter-free, and sedation-free non-invasive imaging methods that mostly use ultrasonography have been developed in order to detect VUR. Any increase in the renal pelvic diameter during voiding is regarded as an indirect sign of VUR. Evans et al. previously reported that an increase in the renal pelvic diameter on post-voiding ultrasonography was not a reliable indicator of VUR9). On the other hand, Hiraoka et al. showed that it detected transient renal pelvic dilation in 70.8% of kidneys with VUR and in 94.1% of the kidneys with high grade VUR10). The sensitivity and specificity of this method for detecting high grade VUR are high; however, it is very time-consuming in non-toilet-trained young children. By using color Doppler ultrasonography, any retrograde flow of urine from the bladder to the ureter is observed on the monitor as a change in color. Koşar et al. revealed that this method had a sensitivity of 89.7% and specificity of 95.1% for the detection of VUR, and these values increased for higher grades of VUR[11)]. However, it is also very time-consuming due to the wait for voiding and is only suitable for toilet-trained children.

Color Doppler ultrasonography also allows for the clear and simple visualization of the ureteral jet, which is actually a bolus of urine being transmitted through the ureter and ejected forcefully into the bladder through the UVJ[2)]. As discussed above, a ureter with a laterally placed ureteral orifice is more likely to be affected by VUR than a ureter with a more medial orifice[1)]. The position of the ureteral orifice is identified by color Doppler ultrasonography, and measurements of the distance from the midline of the bladder to the ureteral orifice may be used as an indirect method to detect VUR. Marshall et al. showed that this distance was significantly longer in pediatric patients with VUR (mean: 10.25 mm) than in those without VUR (mean: 7.98 mm), and a distance > 7 mm was proposed as the cut-off point to predict VUR[12)]. Unfortunately, this was a small study, and no other studies have investigated this method for the detection of VUR.

Furthermore, difficulties are associated with defining a universal and reliable cut-off point to predict VUR because the midline to orifice distance changes with the age of the patient. Ureteral jets have several Doppler waveform patterns based on the number of peaks within a single ureteral jet. Leung et al. classified these patterns into 2 groups: immature monophasic and mature complex jets. Immature monophasic jets are generally detected in children with VUR as well as in younger children, whereas mature complex jets are observed in older children, but not in children with VUR13). Kljucevsek et al. revealed that the overall sensitivity and specificity of this waveform measurement for VUR detection were 88.5% and 82.3%, respectively14). However, this method is only suitable for children older than 3 years because it cannot differentiate whether an immature monophasic jet is a sign of VUR or immaturity itself in younger children14).

Color Doppler ultrasonographic UJA measurements represent a simple and time-saving method that only requires several minutes when the patient is hydrated. Neither sedation nor the wait for voiding is needed in children of any age. Murshal et al. previously reported that no relationship existed between longitudinal or transverse UJA and VUR12). However, their study was small (31 children) and they did not show their detailed procedure or VUR grade. Therefore, most children in that study may have had low grade reflux.

In the present study, we revealed that the UJA value was significantly higher in refluxing renal units than in non-refluxing units, and increased significantly with higher grades of VUR. This result is consistent with the etiology of VUR as well as embryological and anatomical findings of UVJ. VUR is the main underlying disease in children with UTI, particularly infants1). In clinical settings, patients with high grade reflux are at high risk of UTI recurrence and renal scarring, and are less expected to achieve spontaneous resolution with conservative treatment1). Therefore, it is important to detect high grade VUR in younger children, and UJA measurements have good diagnostic validity for detecting grade III-V or grade IV, V VUR with an area under the ROC curve of 0.81 or 0.88, respectively. When a cut-off UJA ≥ 55° was established, grade III-V or grade IV, V VUR was detected with a sensitivity of 85.5% or 94.7%, respectively. Furthermore, a cut-off ≥ 70° diagnosed grade IV, V VUR with a sensitivity of 81.6% and specificity of 82.7%. Therefore, UJA measurements may be of significant clinical value as initial screening tools to detect high grade VUR in children of any age, and the frequency of VCUG may significantly decrease.

Our study is the first to show the efficacy of UJA measurements to detect VUR. However, there were some limitations to this study. This was a preliminary retrospective case series study. We have not yet confirmed precision such as intra-observer and inter-observer agreements, and the influence of bladder volume or hydrated condition in detail. Furthermore, children with obstructing bladder pathologies such as a posterior urethral valve or neurogenic bladder were excluded from this study; however, other functional abnormalities such as dysfunctional voiding may affect the results, because urodynamic examination was not routinely performed in the present study. Therefore, further prospective studies are needed in order to adopt this UJA measurement to actual diagnoses.

Conclusions:

Color Doppler ultrasonographic measurements of the UJA represent a simple and real non-invasive diagnostic method in children of any age, and the UJA value significantly increases with higher grades of VUR. It may be used as a screening tool to detect high grade VUR in pediatric patients.

2,270 words

Conflict of Interest: None

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Legends:

Table 1: Patient characteristics.

Table 2: Characteristics of UJA thresholds.

A, for detecting grade III-V VUR.

B, for detecting grade IV, V VUR.

LR: likelihood ratio.

Figure 1: The ureteral jet direction and angle.

A, The ureteral jet direction and VUR.

B, UJA measurements using color Doppler ultrasonography.

The yellow dashed line and white dashed line indicate the ureteral jet direction and interureteral ridge, respectively.

Figure 2: UJA values.

A, in non-VUR and VUR.

＊$p < 0.0001$ vs. non-VUR.

B, in each VUR grade.

Bars indicate mean values.

＊$p = 0.0002$ vs. grade 0, § $p < 0.0001$ vs. grade 0.

Figure 3: ROC curves of UJA to detect grade I-V, grade III-V, or grade IV, V VUR.

Table 1

April, 2010 - May, 2013
125 patients, 250 renal units

Age: 1 month - 14 years
median; 3.0 years

Gender: 73 boys
52 girls

Chief complaints:
- UTI-febrile; 100 patients
  - -afebrile; 4 patients
- Hydronephrosis; 12 patients
- Others; 9 patients

VUR:
- Non-VUR; 45 patients
- VUR; 80 patients
  - Unilateral 43 patients
  - Bilateral 37 patients

Grade;

0	133 units
I	16 units
II	30 units
III	32 units
IV	30 units
V	9 units

Table 2

A

UJA threshold	Sensitivity	Specificity	LR positive	LR negative
≥ 50°	89.9%	43.4%	1.59	0.23
≥ 55°	85.5%	57.2%	2.00	0.25
≥ 60°	76.8%	64.5%	2.16	0.36
≥ 65°	69.6%	74.7%	2.75	0.41
≥ 70°	62.3%	86.7%	4.70	0.43

B

UJA threshold	Sensitivity	Specificity	LR positive	LR negative
≥ 55°	94.7%	52.3%	1.99	0.10
≥ 60°	92.1%	60.9%	2.36	0.13
≥ 65°	89.5%	71.6%	3.15	0.15
≥ 70°	81.6%	82.7%	4.73	0.22
≥ 75°	68.4%	86.8%	5.18	0.36

Figure 1 A

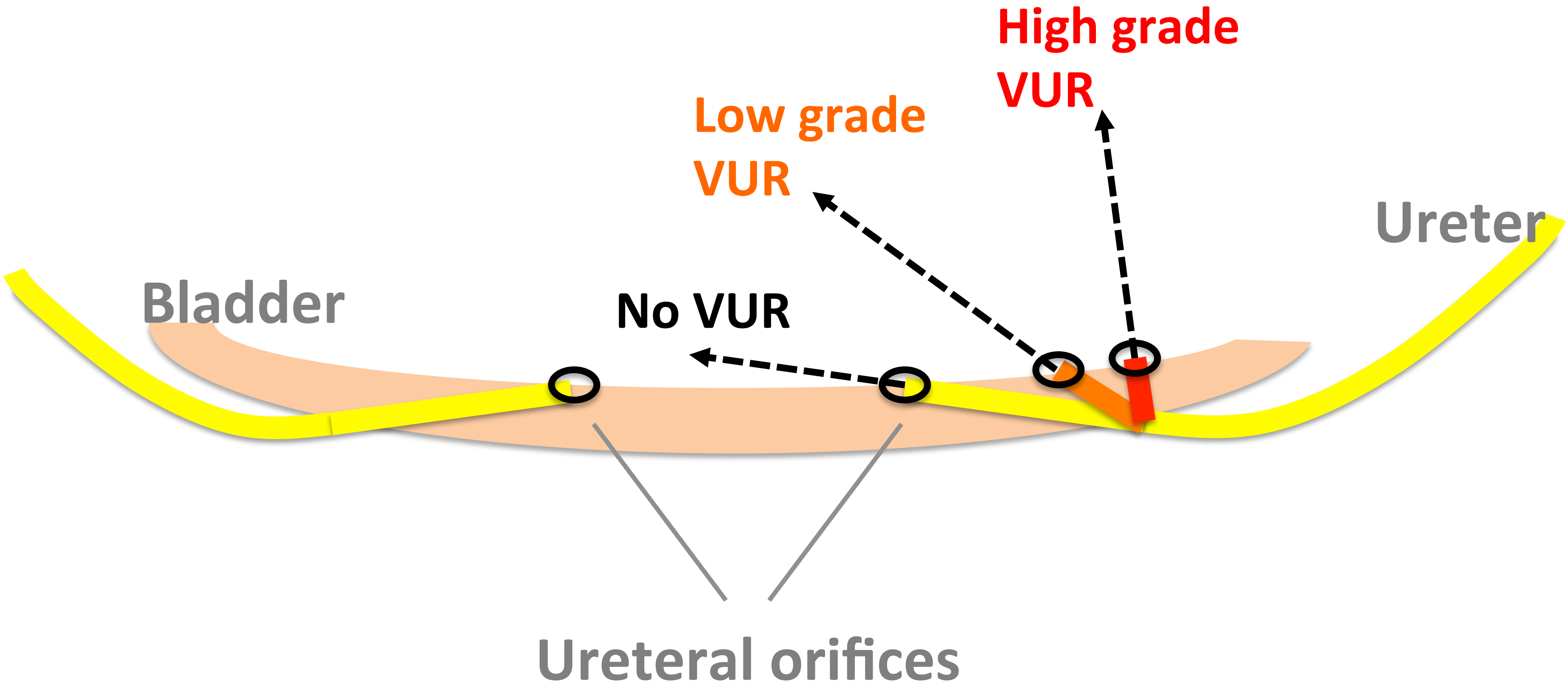

High grade
VUR
Low grade
VUR
Ureter
Bladder
No VUR
Ureteral orifices

Figure 1 B

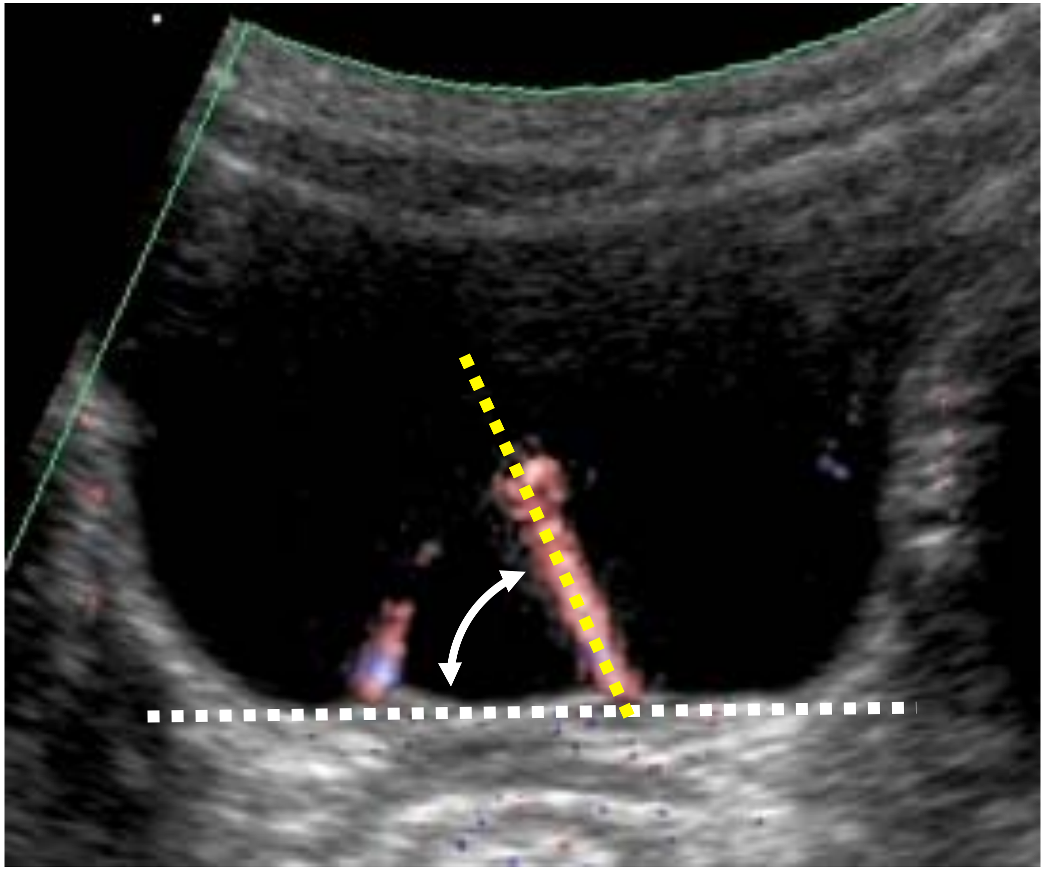


Figure 2 A

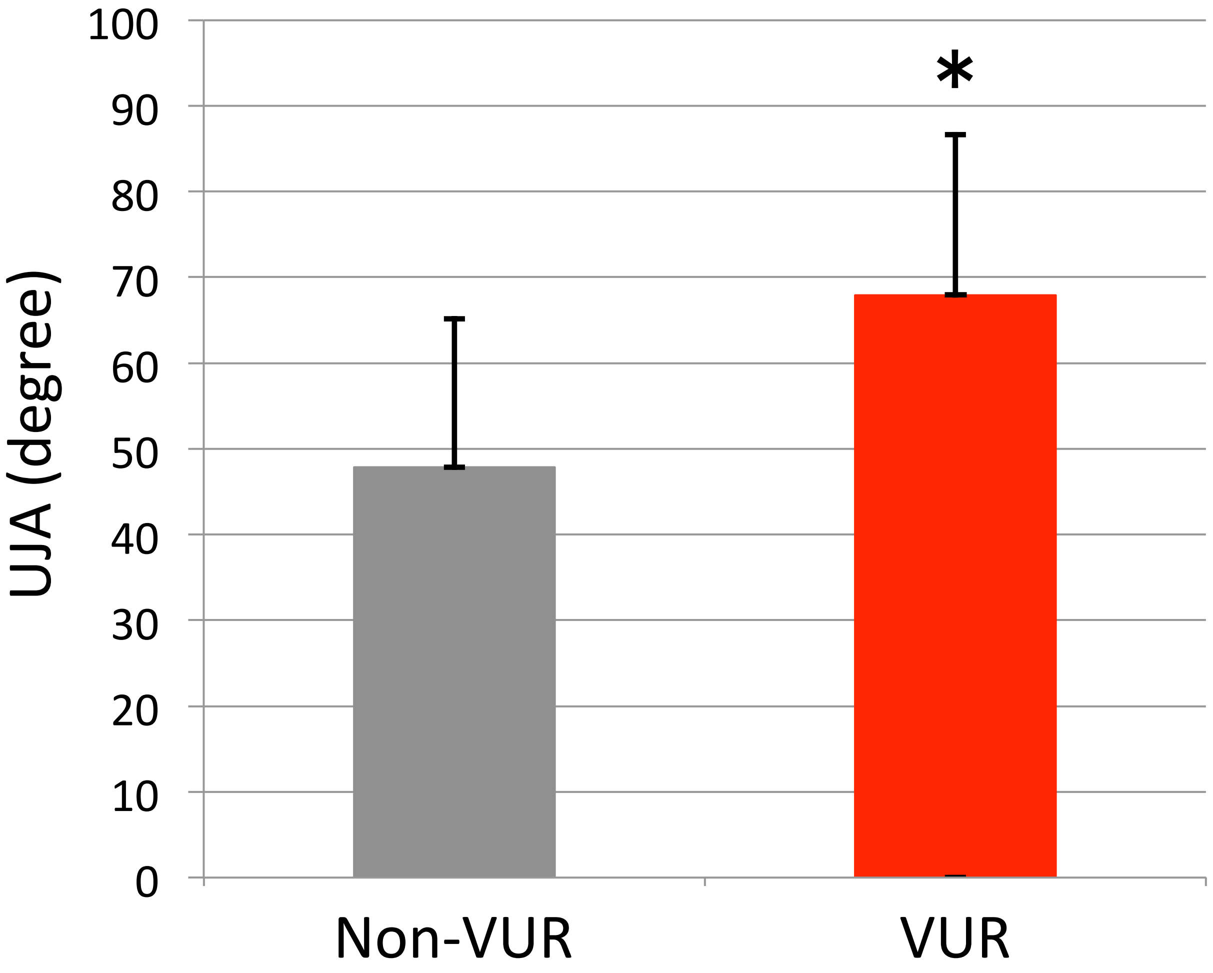


Figure 2 B

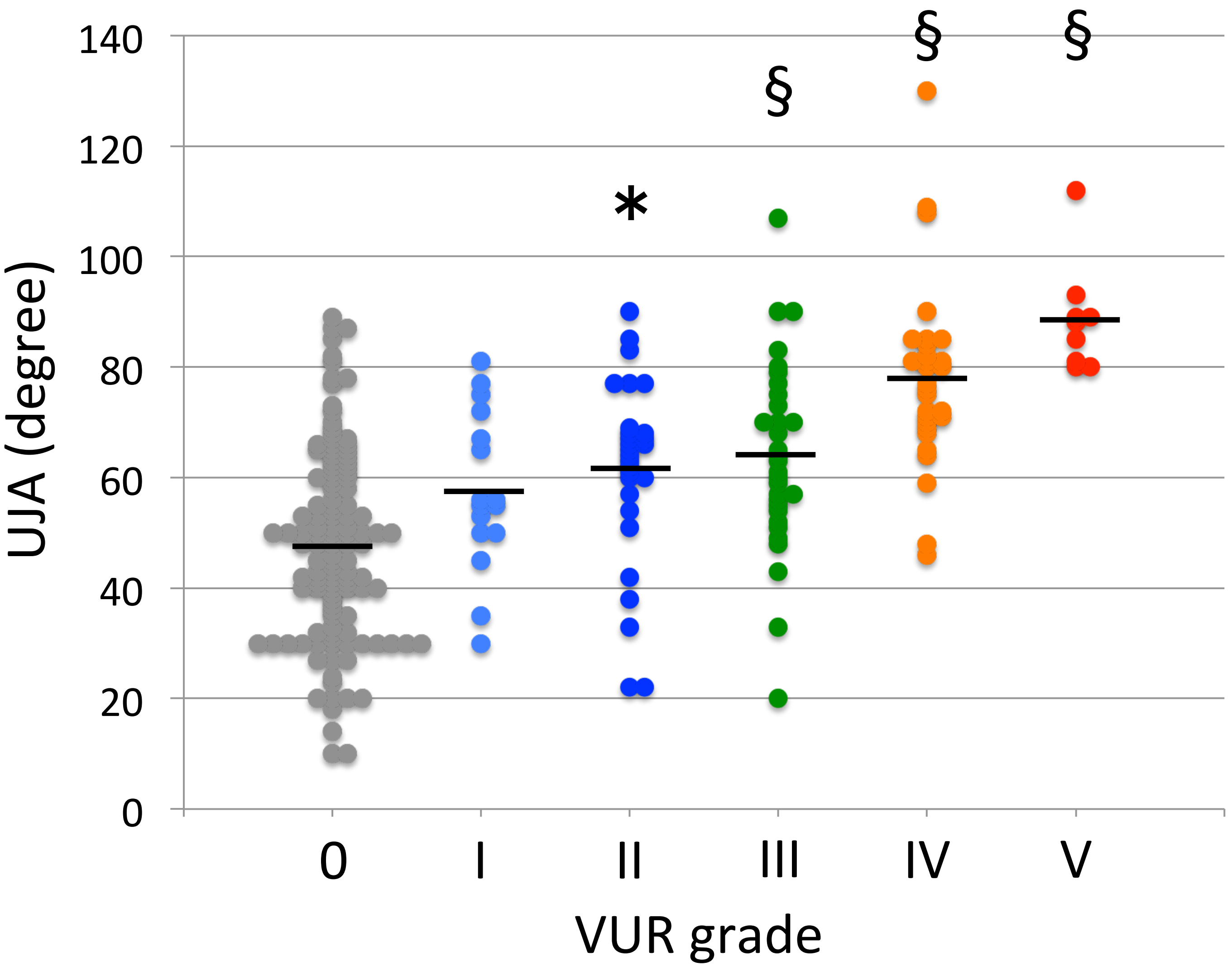
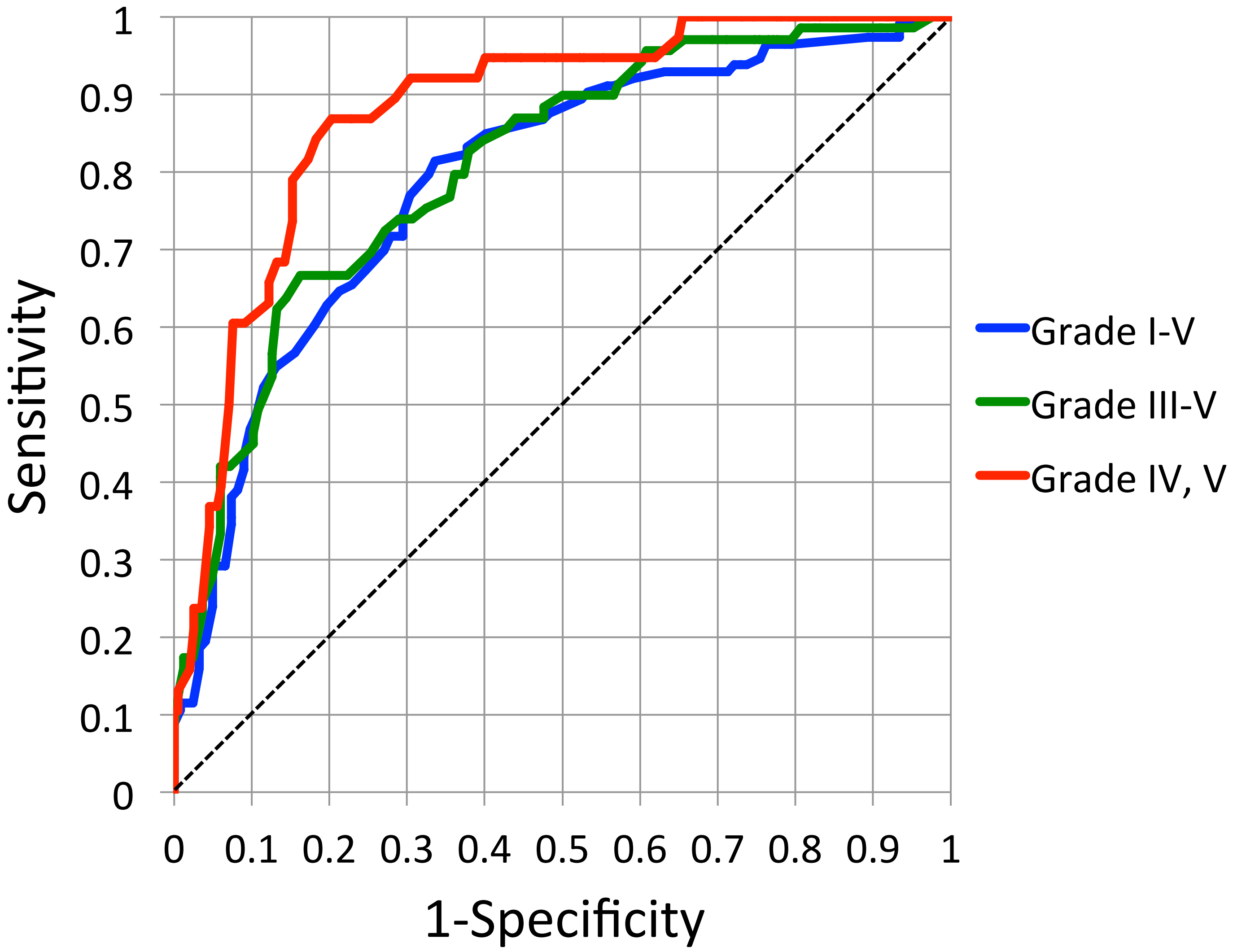


Figure 3


Sensitivity
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1-Specificity
Grade I-V
Grade III-V
Grade IV, V

Abbreviations and Acronyms:

VUR: vesicoureteral reflux

VCUG: voiding cystourethrography

UVJ: ureterovesical junction

UJA: ureteral jet angle

UTI: urinary tract infection

CI: confidence interval

ROC: receiver-operating characteristic